NON-TECHNICAL ABSTRACT

Prostate cancer is the most common internal malignancy diagnosed in US males, resulting in over 41,000 deaths per year. Use of prostate specific antigen (PSA) for screening and widespread education about prostate cancer has resulted in the diagnosis of tumors at earlier stages. However, from 30-50% of men undergoing curative surgery will have a recurrence due in most part to the presence of micro-metastases at the time of definitive therapy. The use of androgen ablation as neo-adjuvant therapy in these patients has failed to improve on the reported recurrence rates. Therefore, strategies to impact on both local tumor and microscopic metastatic lesions is sorely needed. Suicide gene therapy through adenoviral-mediated (ADV) transduction of the Herpes Simplex Virus thymidine kinase gene (HSV-tk) and ganciclovir (GCV) therapy has been shown to impact on a variety of experimental cancers. In a mouse model of prostate cancer, ADV/HSV-tk+GCV resulted in significant growth suppression of the treated primary tumor and in the inhibition of spontaneous metastatic activity. When metastatic deposits were established prior to therapy, ADV/HSV-tk+GCV treatment of a primary prostate tumor can inhibit the further development of these metastases, indicating the induction of systemic anti-tumor activity. The primary goal of this proposal is to utilize ADV/HSV-tk in a Phase I clinical trial in patients with high risk, clinically localized prostate cancer (stage T1c and T2b/c) as neo-adjuvant therapy prior to radical prostatectomy to learn the toxicity profile of this *in situ* treatment approach. Prostate tumors will be injected with the escalating doses of vector in 3 patient tiers. All patients will receive a 7 day course of GCV during which time patients will be monotored for potential toxicities as inpatients. Patients will then undergo the pre-scheduled prostatectomy 7-10 days later. Since all patients will undergo lymph node dissection and removal of the prostate following treatment valuable information can be gleaned from an analysis of these tissues. These studies will determine the presence and spread of vector and document the induction of cytotoxicity within the treated prostate. The induction of immune activity against the adenovirus or the *tk* gene may affect the efficacy of this treatment. The induction of immunity against the ADV/HSV-tk will be tested in lymphocytes found within the tumor, removed lymph nodes and the blood. These results may have far reaching ramifications for adenoviral mediated gene therapy. Therefore, this study will not only provide important information regarding the potential toxicity and efficacy of this treatment but immunological activity induced against the adenovirus and/or transgene.